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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/337,675 | 06/22/1999 | RAJEEV A. JAIN | 029318/0497 | 9275 |

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| EXAMINER |
|---|
| PULLIAM, AMY E |

| ART UNIT | PAPER NUMBER |
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| 1615 | 31 |

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/337,675 | JAIN ET AL. | |
| | Examiner | Art Unit | |
| | Amy E Pulliam | 1615 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *1/15/03* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-22 and 25-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22,25-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Receipt of Papers*

Receipt is acknowledged of the Request for Extension of Time, the Amendment D, and the Declaration, all received by the Office January 15, 2003.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-22, and 25-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,145,684 to Liversidge *et al.* (hereinafter Liversidge).

Liversidge discloses dispersable particles made of a drug substance and a surface modifier adsorbed on the surface of the drug, to maintain an effective average particle size of less than about 400 nm, as well as the method of making the particles through wet grinding. Further, Liversidge teaches that of pharmaceutical formulations containing the nanoparticles, and their use in method of treating mammals (abstract). Liversidge further discloses the drug substance useful in this invention is a poorly soluble drug, chosen from the list in column 3, lines 53+. In addition, Liversidge teaches that the surface modifier of the invention can be selected from various polymers, oligomers, natural products and surfactants. Examples of excipients include gelatin, casein, lecithin, gum acacia and others, and examples of polymers include carboxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose and others (c 4, l 34-

55). Liversidge also teaches that pharmaceutical compositions according to this invention include the nanoparticles and a pharmaceutically acceptable carrier, which is well known in the art for making solid or liquid oral formulation (c 7, l 53-60).

]Liversidge does not teach the specific amounts of excipients present in the composition, however, it is the position of the examiner that based on the general teaching of the presence of excipients, and the teaching that Liversidge's composition can be formulated into well known forms, including solid oral forms, it is the position of the examiner that the specific concentrations is a specific limitations which would be routinely determined by one of ordinary skill in the art through minimal experimentation, as being suitable, absent the presentation of some unusual and/ or unexpected results. The results must be those that accrue from the specific limitations.

Further, it is the position of the examiner that the teaching of cellulose polymers in the composition reads on applicant's claim to both a surface stabilizer and a rate controlling polymer, because on page 12, lines 27-28, applicant states that a suitable surface stabilizer includes various polymers, therefore the cellulose polymers can perform both desired functions. One of ordinary skill in the art would have been motivated to produce a well known pharmaceutical dosage form, such as a tablet, which incorporates Liversidge's nanoparticles, and the necessary excipients, especially based on Liversidge's disclosure that his particles are intended for this exact purpose. One of ordinary skill in the art would expect a successful pharmaceutical dosage form.

Liversidge teaches the surface modifiers at column 4, lines 34-55. Furthermore, Liversidge teaches the broad categories of drugs at column 3, lines 53-68. Liversidge does not

teach the specific drugs claimed by applicant. However, it is the position of the examiner that because the reference teaches the same broad drug categories claimed by applicant, one of ordinary skill in the art would have been motivated to use any well known drug which falls within one of those broadly taught categories, because there has been no evidence provided that some drugs behave better than others. The expected result would be a successful pharmaceutical formulation.

Applicant has added two new claims. The first is drawn to several different forms for the nanoparticulate composition. This claim is suggested by the reference, because the reference teaches mixing a polymer and a drug, which suggests the second option in the claim.

Therefore, this invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1 , 10 , and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge, as discussed above, in view of WO 95/22318 to Vernon OR US Patent 5,188,755 to Chang *et al.*.

Liversidge *et al.* do not specifically teach each of the polymers claimed by Applicant. However, as stated previously, Applicant claims a large number of polymers which can be successful in their formulation, as shown in claim 10. Liversidge *et al.* teach many of these polymers, as discussed in the first rejection, however, the reference does not teach the specific polymers of new claim 54. Vernon and Chang are relied upon to show that the polymers rate controlling polymers are well known in the art and are often substituted for one another.

Vernon teaches a controlled release formulation for use with a variety of drugs, wherein the polymer matrix is made from PVA, HEC, HPC, HPMC, PEG, polyethylene oxide, or others (abstract).

Chang is also relied upon for the teaching of equivalency between hydroxypropyl cellulose and polyethylene oxide (c 2, l 20-23).

It is the position of the examiner that one of ordinary skill in the art would have been motivated to use any well known polymer in the teachings of Liversidge *et al.*, particularly because these polymers are known to be interchangeable in the art. The expected result would be a successful pharmaceutical nanoparticulate composition, with the same benefits taught by Liversidge. Therefore, this invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's arguments have been fully considered but are not found to be persuasive. Applicant argues that Liversidge does not teach nanoparticles in a controlled release formulation. First and foremost, the examiner again points out that there is nothing in the reference which declares that the formulation is an immediate release formulation. Applicant has included a broad range for the release time, from about 2 hours to about 24 hours. Absent a showing to the contrary, it is impossible for the examiner to be certain that the formulations of Liversidge *et al.* do not fall within this very broad range. This justifies the examiner's request for comparative analysis, if Applicant wishes to prove that the reference *is* immediate release.

Applicant refers to the Declaration of Dr. Rejeev Jain for the majority of their arguments. The declaration describes two examples, one being an immediate release formulation and the

other being a delayed release formulation. Applicant asserts that the two examples are identical, except that the delayed release formulation additionally contained a coating of polyvinyl acetate phthalate as a controlled release polymer. The examiner does not find this comparison persuasive for several reasons. First, the examiner finds no indication that the immediate release formulation is drawn from Liversidge *et al.*. Furthermore, the examiner phoned Applicant's representative to clarify this matter, and was given no further guidance as to how the example in the declaration relates to the cited prior art reference. Absent evidence that the comparison was made between an actual composition of Liversidge versus an actual composition of Applicant's, the data cannot be found persuasive. To date, there has been no conclusive evidence provided that Liversidge is actually an immediate release formulation. In order to do this, Applicant should use an actual formulation from Liversidge, and show its release rates in comparison to an actual formulation of Applicant's. Additionally, the declaration is not commensurate in scope with the present claims. The declaration discloses a very specific formulation, comprising a specific drug, specific excipients, and a particular polymer. The independent claim requires only a drug, a stabilizer, and a polymer; the claim requires no particular components. Furthermore, claim 1 allows the polymer to either be integrated in the matrix with the drug, OR coat the drug, and the example in the declaration only shows the polymer coating the drug. In order for a declaration to be persuasive, it must (1) be commensurate in scope with the claims, (2) provide statistical analysis of the data, and (3) show that any differences between the prior art and the present invention are present in the claims.

Additionally, the examiner maintains that Applicant's present claims are very broad. Based on the data provided in the declaration, and in statements made in Applicant's response, it

appears that the success of the controlled release formulation requires much more than the few limitations found in the present claim. For example, in the declaration, Applicant discusses the necessity for an intermediate coating. This is not found in the instant claim language, but appears to be a vital part of the invention. Additionally, Applicant states that there are "inherent difficulties of designing controlled release active agent products," and that "nanoparticulate active agents generally act very quickly to due to their large surface area." Applicants themselves have admitted that the success of a nanoparticulate composition can depend greatly on the drug, and that generally, nanoparticulate drugs tend to act quickly. This reaffirms the examiner's position that the declaration presented is not commensurate in scope with the instant claims, as the declaration only shows success with one drug, and only shows success with the polymer coating the drug. This is not persuasive with regards to the broad scope of the claims.

The examiner points out that the phrase "controlled release" in the preamble is not given patentable weight. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). It is recommended that Applicant narrow the claims to more clearly define the scope of their invention.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E Pulliam whose telephone number is 703-308-4710. The examiner can normally be reached on Mon-Thurs 7:30-5:00, Alternate Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on 703-308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3592 for regular communications and 703-305-3592 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

A. Pulliam
Patent Examiner
April 4, 2003

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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